

REMARKS

Claims 1-10 and 12-22 were pending in the present application. Claims 3-10 and 14-22 were withdrawn from consideration. By virtue of this response, claims 2, 16, 17, and 20 are amended and claims 3-11, 14, 19 and 21-22 have been cancelled.

The specification has been amended to include the "Cross-Reference to Related Applications" paragraph on page 1. For the clarity of the record, Applicants note that the cross-reference paragraph recites the priority application listed on the face of the PCT application as published and in the inventor oath/declaration filed on February 28, 2007. Applicants note that the Official Filing Receipt correctly lists Australian Application No. 2003905551 filed October 10, 2003, but includes a typographical error in the serial number of Australian Application No. 2003906658 filed December 1, 2003 (listed as 20033906658). The same error is found in the Examiner's remarks in numbered paragraph 5 of the present Office Action. The Application Data Sheet filed with the Office on June 3, 2009 correctly lists the Australian Application No. 2003906658 priority application. A corrected Official Filing Receipt will also be requested. The Office is respectfully requested to update Office databases with the information as provided on the Application Data Sheet.

Support for the amended claims can be found throughout the specification, including the claims, as originally filed. In particular, claims 16-17 and 20 have been amended to remove improper dependencies and update the claim format for the antecedent basis of claim 1, as amended. Claim 3 has been amended to render the claim more consistent with US practice Markush group wording.

No new matter is believed to have been added by way of these amendments.

Regarding the Status of the Claims

Upon review of the restriction requirement mailed March 3, 2008, Applicants note that claims 16-22 were objected to under 37 CFR 1.75(c) as being in improper form for

containing multiply dependent claims depending from a multiply dependent claims and were therefore not considered in the restriction requirement issued.

Withdrawn claims 16-18 and 20 are presently amended, as needed, to remove improper dependencies. Each of these claims ultimately depends from claim 1, and therefore incorporates all of the limitations of claim 1. Claim 16 is a pharmaceutical formulation of the antibody of claim 1. Claims 17-18 and 20 are directed to methods of using the isolated antibody of claim 1. Applicants respectfully request that the Examiner set forth in the record whether such amended claims can be considered to be part of the elected group V, drawn to the product of isolated antibodies, or whether the Examiner chooses to restrict between group V (a product) and claims 17-18 and 20 (methods of using the product). Should the Examiner consider claims 16, or 17-18 and 20 to form one or more separate group of claims, Applicants note for the record that Applicants should be entitled to either a) request rejoinder of the product and method claims as being related as product and process for use, should claim 1 be found allowable (*see* MPEP § 821.04 regarding withdrawn process claims that depend from or otherwise include all the limitations of the patentable product claims may be rejoined) or b) should be entitled to file one or more divisional patent applications right under 35 U.S.C. § 121 directed to the subject matter of claims 16 or 17-18 and 20.

Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Rejections under 35 USC §102

Claims 1-2 and 11-13 are rejected under 35 U.S.C. §102(b)¹ as allegedly being anticipated by Briskin *et al.* (US 20020151026 A1). Applicants traverse this rejection.

Regarding the alleged anticipation of the pending claims by Briskin *et al.*, the Applicants respectfully submit that the Office has not established a *prima facie* case that Briskin *et al.* teaches each and every limitation of the currently pending claims, either implicitly or explicitly; and, therefore, the Office has not met its burden for denying the patentability of the pending claims under 35 U.S.C. § 102.

As an initial matter Applicants note that while Briskin *et al.*, generically disclose the possible preparation of antibodies to the polypeptide encoded by the disclosed nucleic acid sequence mammalian hyaluron synthase (HAS) (*see* ¶62) and disclose the notion that being able to bind mammalian HAS polypeptide with high affinity is desirable (*see* ¶63), nowhere in the Examples or detailed description does Briskin *et al.*, demonstrate that anti-HAS antibodies were/could be generated with the characteristics cited in claim 1 (and therefore its dependent claims) and neither does Briskin *et al.*, exemplify that anti-HAS antibodies of particular specificity or affinity can be generated. There is no disclosure relating to generation of anti-HAS antibodies *selective for particular regions/fragments of the HAS sequence* (*e.g.*, SEQ ID NO:25), nor any indication of a desirability for doing so. Indeed, Applicants note that Figures 3B and 3D, which depict the proposed structure of HAS polypeptide, teach that Briskin *et al.*, SEQ ID NO:2 residues 515-525 (residues 529-539 of “consensus numbering scheme”), which correspond to SEQ ID NO:25 recited in the present claims, are located partially in an *intracellular* loop and partially in a transmembrane region. As would be appreciated by the

¹ For the clarity of the record, Applicants note that Briskin *et al.*, as cited (US 20020151026 A1) was published on October 17, 2002, while Applicants earliest priority date is October 10, 2003, less than 1 year after publication of Briskin *et al.*, therefore, this reference is available as a reference under 35 U.S.C. 102(a)/102(e). However, Applicants note that the priority document, of which the present Briskin *et al.*, reference is a divisional application (USSN 08/635,552), issued as US 6,423,514 on July 23, 2002.

skilled artisan based on the teachings of Briskin *et al.*, as the residues in SEQ ID NO:25 are depicted either within a transmembrane region or intracellular loop, they would be sequestered from interaction with the extracellular environment and amino acids in this region would be unlikely to be used to generate anti-HAS antibodies capable of reducing HAS activity.

Indeed, the only actual antibodies used in Briskin *et al.* are monoclonal antibodies anti-murine CD44 TJB1.7 (a gift from T. Yoshino and E. Butcher, Stanford, Calif.); anti-murine MAdCAM-1 MECA-367 (Stretter, P.R., et. al., Nature 331:41-46 (1988)); Anti-human VCAM-1 2G7 (Graber, N., J. Immunol (145):819 (1990)); anti-murine $\beta 7$ FIB 504 (Andrew, D.P., et.al., J. Immunol. 153:3847-3861 (1994)); anti-murine $\alpha 4$ PS/2 (Miyake, K., J. Exp. Med. 173:599-607 (1991) (see ¶¶ 72-73 and 80-81). *See below*:

- anti-murine CD44 TJB1.7 is an antibody to CD44 an hyaluronan **binding receptor**.
- anti-murine MAdCAM-1 MECA-367 is an antibody to MAdCAM-1 a mouse **immunoglobulin**
- anti-human VCAM-1 2G7 is an antibody to VCAM-1 a human **immunoglobulin**
- anti-murine $\beta 7$ FIB 504 is an monoclonal antibody to an **integrin $\beta 7$ receptor**
- anti-murine $\alpha 4$ PS/2 is an monoclonal antibody to an **integrin $\alpha 4$ receptor**.

None of these antibodies are anti-HAS antibodies, let alone anti-HAS antibodies that specifically target SEQ ID NO:25, as recited in the presently pending claims.

Further, the Examiner states at numbered paragraph 9, page 3, of the present Office Action that:

In response to Applicant's arguments that Briskin et al. did not teach an antibody that specifically targets SEQ ID NO:25, it is noted that Briskin's antibody reduced the level of hyaluron synthase activity (see paragraph 0062). Given that the prior art antibody has the same functional activity as the antibody of the present invention, it is *more likely than not* that the prior art antibody would bind to SEQ ID NO:25 in order to inhibit HAS.
(*Emphasis added.*)

Applicants note that, as clarified above, Briskin *et al.* *did not* prepare any anti-HAS antibodies and therefore there is no exemplified Briskin *et al.*, antibody that “reduced the level of hyaluron synthase activity (see paragraphs 0062).” Further, there is no “Briskin *et al.* antibody that *has* the same functional activity” with regard to reduction of HAS activity and no antibodies demonstrating the same sequence specificity as the presently claimed antibodies. Further, there is no direction to the skilled artisan to select the particular sequence of SEQ ID NO:25 of the HAS sequence for generation of antibodies selective for this region.

With regard to the Examiner’s comment regarding “it is *more likely than not* that the prior art antibody would bind to SEQ ID NO:25 in order to inhibit HAS” as quoted above, Applicants note that the Examiner appears to be setting forth the argument that the antibody property of specifically targeting SEQ ID NO:25 would be an “inherent” property of the antibodies described in Briskin *et al.*

In the present application, claim 1, and therefore its dependent recites that the claimed antibodies reduces the level of HAS activity *and* the antibody specifically targets SEQ ID NO:25 within an HAS. Briskin *et al.*, does not explicitly teach the specific targeting of SEQ ID NO:25, and therefore does not disclose every limitation of the currently pending claims; thus, the Office must rely on the proposition that the claim limitations not explicitly disclosed are instead inherent properties of the reference antibodies in order to establish a *prima facie* case of anticipation. However, the Office’s reliance on inherent anticipation to establish unpatentability is factually incorrect, because the properties *are not in fact inherent* under the legal standard, thus the *prima facie* case of anticipation fails.

As noted above, the reference does not teach anti-HAS antibodies that specifically target SEQ ID NO:25 within an HAS. The reference does not teach this limitation and there is no extrinsic evidence to support a finding of inherency (see below), particularly for antibodies not actually made.

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. (*In Continental Can Company USA, Inc. vs Monstanto Co.* 948 F.2d 1264, 1268, 20 USPQ2d 1746 (Fed. Cir. 1991) *Emphasis Added*)

IV. EXAMINER MUST PROVIDE RATION-ALE OR EVIDENCE TENDING TO SHOW INHERENCY

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). ***"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'"*** *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted) (The claims were drawn to a disposable diaper having three fastening elements. The reference disclosed two fastening elements that could perform the same function as the three fastening elements in the claims. The court construed the claims to require three separate elements and held that the reference did not disclose a separate third fastening element, either expressly or inherently.). >Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species. (*Emphasis Added*))

As is well known in the art, merely generating antibodies by techniques known to the skilled artisan (in the absence of any specific teachings in Briskin *et al.* regarding antibody generation) does not provide a *certainty* that an antibody that specifically binds to SEQ ID NO:25 as recited in the claims will be produced.

As further detailed below, the Office's reliance on inherent anticipation to establish

unpatentability is factually incorrect, because the properties *are not in fact inherent* under the legal standard. Thus, the *prima facie* case of anticipation fails (*see below, Ex parte Levy*, 17 USPQ2d 1461, 1462-1464 (Bd. Pat. App. & Int. 1990)).

[1] **The factual determination of anticipation requires the disclosure in a single reference of every element of the claimed invention.** *In re Spada*, —F.2d —, 15 USPQ2d 1655 (Fed.Cir. 1990); *In re Bond*, —F.2d —, 15 USPQ2d 1566 (Fed.Cir. 1990); *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 7 USPQ2d 1315 (Fed.Cir. 1988); *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 7 USPQ2d 1057 (Fed.Cir. 1988); *Alco Standard Corp. v. TVA*, 808 F.2d 1490, 1 USPQ2d 1337 (Fed.Cir. 1986); *In re Marshall*, 578 F.2d 301, 198 USPQ 344 (CCPA 1978); *In re Arkley*, 455 F.2d 586, 172 USPQ 524 (CCPA 1972). **Moreover, it is incumbent upon the examiner to identify wherein each and every facet of the claimed invention is disclosed in the applied reference.** *Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick*, 730 F.2d 1452, 221 USPQ 481 (Fed.Cir. 1984). (*Ex parte Levy*, 17 USPQ2d at 1462, **Emphasis Added.**)

[2] The examiner also relies upon the theory that Schjeldahl's catheter balloon is inherently biaxially oriented. On page 4 of the Answer, the examiner points out that inasmuch as the Patent and Trademark Office does not have the requisite laboratory equipment for testing, the burden shifts to appellant. **However, the initial burden of establishing a *prima facie* basis to deny patentability to a claimed invention rests upon the examiner.** *In re Piasecki*, 745 F.2d 1468, 223 USPQ 785 (Fed.Cir. 1984). **In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.** *In re King*, 801 F.2d 1324, 231 USPQ 136 (Fed.Cir. 1986); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed.Cir. 1983); *In re Oelrich*, 666 F.2d 578, 212 USPQ 323 (CCPA 1981); *In re Wilding*, 535 F.2d 631, 190 USPQ 59 (CCPA 1976); *Hansgirk v. Kemmer*, 102 F.2d 212, 40 USPQ 665 (CCPA 1939). In our opinion, the examiner has not discharged that initial burden. (*Ex parte Levy*, 17 USPQ2d at 1463-1464, **Emphasis Added**)

With regard to the recited property of the claimed anti-HAS antibodies of reducing the level of HAS synthesis, Applicants draw the Examiner's attention to WO 2007/11245 (included in the present SIDS). In WO 2007/11245 antibodies are generated in the presence of peptide antigens (HAS 418 (INT-1); HAS 419 (Ex-1) and HAS-421 (INT-2), *see* Table 2, pg. 32 for sequences and also Table 7, Example 23 of the present application³) and therefore are

² Applicants note the antibodies generated in Example 23 of the present application are further characterized in WO 2007/11245.

“specific” for those peptide sequences. As the skilled artisan will appreciate, HAS 419 (Ex-1) is a peptide corresponding to SEQ ID NO:25. As shown in Figure 8 of WO 2007/11245, not all anti-HAS antibodies can inhibit HAS activity in particular cell types (*e.g.*, in MD-MBA-241 cells INT-2 and Ex-1 do, INT-1 does not. Further, Table 3 of WO 2007/11245 provides evidence that not all antibodies raised against regions of HAS sequence interact with various cell types and thus every anti-HAS antibody does not necessarily reduce HAS activity. For example, antibodies raised against INT-1 reacted with none of the five cell types tested, antibodies raised against INT-2 reacted with four of five cell types tested, while EX-1 reacts with all five cell types (this sequence corresponding to SEQ ID NO:25). Thus, the mere suggestion that antibodies be generated against “HAS” as disclosed in Briskin *et al.*, does not necessarily mean that antibodies so generated would definitely possess the recited functional characteristics of the claimed antibodies (reduction of HAS activity and specific targeting of SEQ ID NO:25).

Applicants assert that the Office has erred in setting forth the rejection under 102(b) in view of Briskin *et al.* in that the Office has not, as noted above, established a *prima facie* case under 35 U.S.C. §102(b) and, further, that, even if the Office had established a *prima facie* case of unpatentability, the Applicants have, in fact, rebutted the case as set forth by the Office. Namely, as quoted in MPEP 2112.01 “. . . the *prima facie* case can be rebutted by evidence showing that the prior art products *do not necessarily possess the characteristics of the claimed product*. In *re Best*, 562 F.2d at 1255, 195 USPQ at 433. MPEP 211.01.” (Emphasis added, in part.)

In view of the above remarks, Applicants respectfully request withdrawal of the rejections under 35 USC §102.

Rejections under 35 USC §103

Claims 1-2 and 12-13 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Briskin *et al.* in view of Falkenberg *et al.* (J. Clin. Chem. Clin. Biochem.

1984, 22:867-882) and Owens *et al.* (Journal of Immunological Methods, 1994, 168:149-165). Applicants respectfully traverse the rejection.

As noted by the Examiner, Owens *et al.* and Falkenberg *et al.* are representative of the state of antibody technology. More specifically they related to the making of monoclonal, polyclonal and humanized antibodies. However, Applicants assert that neither Owens *et al.* nor Falkenberg *et al.* provide the teaching lacking in Briskin *et al.* as described above regarding the generation and selection of antibodies with the characteristics recited in claim 1 (and therefore its dependent claims); that is, antibodies that selectively target SEQ ID NO:25. And, further, as noted in MPEP 2141.02(V) (*see below*), obviousness cannot be based on that which is not known at the time the invention is made:

Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).

As stated above with respect to the rejection under 35 U.S.C. §102(b), Applicants rebut the premise that the teachings of Briskin *et al.* inherently disclose the antibodies presently claimed and, even if Briskin *et al.* did inherently produce antibodies with the characteristics presently claimed, such disclosure could *not* serve as the basis for an obviousness rejection.

In addition, as noted above, Briskin *et al.* teach that the sequence corresponding to SEQ ID NO:25 is found within a putative transmembrane/intracellular-loop region of topology for HAS and therefore Briskin *et al.* in fact would “teach away” for the selection of antibodies which specifically target SEQ ID NO:25. *See also* MPEP 2141.02 (I), as quoted below:

I.THE CLAIMED INVENTION AS A WHOLE MUST BE CONSIDERED

In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is *not whether the differences themselves would have been*

*obvious, but whether the claimed invention as a whole would have been obvious. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); Schenck v. Nortron Corp., 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983) (Claims were directed to a vibratory testing machine (a hard-bearing wheel balancer) comprising a holding structure, a base structure, and a supporting means which form "a single integral and gaplessly continuous piece." Nortron argued the invention is just making integral what had been made in four bolted pieces, improperly limiting the focus to a structural difference from the prior art and failing to consider the invention as a whole. **The prior art perceived a need for mechanisms to dampen resonance, whereas the inventor eliminated the need for dampening via the one-piece gapless support structure. "Because that insight was contrary to the understandings and expectations of the art, the structure effectuating it would not have been obvious to those skilled in the art."** 713 F.2d at 785, 218 USPQ at 700 (citations omitted).). (**Emphasis added.**)*

Thus, for at least the reasons recited above, Applicants believe that claim 1, and therefore its dependent claim is not obvious in view of Owens *et al.* and Falkenberg *et al.* in combination with Briskin *et al.*

Request for Examiner Interview

Should the remarks presented herein not address the Examiner's concerns, she is respectfully requested to contact the undersigned prior to the issuance of a further action.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **229752006000**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: July 20, 2009

Respectfully submitted,

Electronic signature: /Kimberly A. Bolin/
Kimberly A. Bolin
Registration No.: 44,546
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304-1018
(650) 813-5740